AUSTRALIAN PRODUCT INFORMATION

SYMTUZA®

DARUNAVIR/COBICISTAT/EMTRICITABINE/TENOFOVIR ALAFENAMIDE

FILM-COATED TABLETS

1. NAME OF THE MEDICINE

Darunavir/cobicistat/emtricitabine/tenofovir alafenamide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SYMTUZA 800/150/200/10 mg tablets contain 800 mg of darunavir (as 867 mg darunavir ethanolate), 150 mg of cobicistat (as 288.5 mg of cobicistat on silicon dioxide), 200 mg of emtricitabine and 10 mg of tenofovir alafenamide (as 11.2 mg tenofovir alafenamide fumarate).

For a full list of excipients, see **section 6.1** List of excipients.

3. PHARMACEUTICAL FORM

SYMTUZA is supplied as a 2.2 x 1.1 cm, yellow to yellowish brown, capsule-shaped, film-coated tablet, debossed with “8121” on one side and “JG” on the opposite side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SYMTUZA is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Genotypic testing should guide the use of SYMTUZA (see **section 4.2** Dose and method of administration, **section 4.4** Special warnings and precautions for use and **section 5.1** Pharmacodynamic properties).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose in adults

The recommended dose of SYMTUZA is one tablet taken once daily with food.

Dose in adolescents (12-17 years of age)

In adolescent patients aged 12 years and older weighing at least 40 kg, the recommended dosage is one tablet taken once daily with food. No dose has been established for SYMTUZA for paediatric patients 3-11 years of age or weighing less than 40 kg (see **section 5.2** Pharmacokinetic properties, Special populations). SYMTUZA should not be used in paediatric patients below 3 years of age in view of toxicity observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age (see **section 5.3** Preclinical safety data).

Dose in elderly (65 years of age and older)

Limited information is available on the use of SYMTUZA in patients aged 65 and over (see **section 5.2** Pharmacokinetic properties, Special Populations). Therefore, SYMTUZA should be used with caution in elderly patients.

Method of administration

SYMTUZA should be administered orally once daily with food. The type of food does not affect the exposure to the components of SYMTUZA (see **section 5.2** Pharmacokinetic Properties, Absorption). SYMTUZA should be swallowed whole without breaking or crushing to ensure administration of the entire dose. For patients who are unable to swallow the whole tablet, SYMTUZA may be split into two pieces using a tablet-cutter, and the entire dose should be taken with food immediately after splitting.

If a dose of SYMTUZA is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of SYMTUZA with food as soon as possible. If a missed dose is noticed later than 12 hours after the time it is usually taken, it should not be taken and the patient should resume the usual dosing schedule.

After therapy with SYMTUZA has been initiated, patients should not alter the dosage or discontinue therapy without instruction of their healthcare provider. Separate pharmaceutical forms of the components of SYMTUZA are available, either alone or in combination products. Therefore, if patients are unable to swallow the SYMTUZA tablet, require a dose modification of any of the components of SYMTUZA, or discontinue treatment with SYMTUZA, alternatively, the pharmaceutical forms of the individual components may be used. Please refer to the respective Product Information for proper use of these products.

Dosage adjustment

Hepatic insufficiency

No dose adjustment of SYMTUZA is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

SYMTUZA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and there are only limited data regarding the use of SYMTUZA components in this population, therefore, specific dosage recommendations cannot be made. SYMTUZA should be used with caution in patients with severe hepatic impairment (see **section 5.2** Special populations).

Renal insufficiency

SYMTUZA should not be initiated in patients who have an estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance ($eGFR_{CG}$) below 30 mL/min (see **section 5.2** Special populations).

SYMTUZA should be discontinued in patients with $eGFR_{CG}$ that declines below 30 mL/min during treatment.

No dose adjustment of SYMTUZA is required in patients with an $eGFR_{CG}$ of 30 mL/min or above.

Pregnancy and postpartum

Treatment with darunavir/cobicistat (two of the components of SYMTUZA) during pregnancy results in low darunavir exposure (see **section 5.2** Special populations). Therefore, therapy with SYMTUZA should not be initiated during pregnancy, and women who become pregnant during therapy with SYMTUZA should be switched to an alternative regimen (see **section 4.6** Fertility, pregnancy and lactation, Use in pregnancy). Darunavir/ritonavir in combination with emtricitabine/tenofovir alafenamide may be considered as an alternative.

4.3 CONTRAINDICATIONS

Hypersensitivity to darunavir, cobicistat, emtricitabine, tenofovir alafenamide, or to any of the excipients.

Darunavir and cobicistat are both inhibitors of the cytochrome P450 3A (CYP3A) isoform. SYMTUZA should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). Examples include alfuzosin, antiarrhythmic drugs (e.g. amiodarone, bepridil, disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone, quinidine), apixaban, astemizole, cisapride, colchicine (in patients with renal and/or hepatic impairment), dapoxetine, dronedarone, elbasvir/grazoprevir, ergot alkaloids (e.g., dihydroergotamine, ergotamine, ergonovine and methylergonovine), ivabradine, lomitapide, lovastatin, lurasidone, naloxegol, oral midazolam, pimozide, ranolazine, sildenafil (when used for treatment of pulmonary arterial hypertension), simvastatin, terfenadine and triazolam (see **section 4.5** Interactions with other medicines and other forms of interactions).

Darunavir and cobicistat are both substrates of the cytochrome P450 3A (CYP3A) isoform. Co-administration of SYMTUZA with CYP3A inducers is expected to lower plasma concentrations of darunavir and cobicistat which may lead to loss of efficacy of darunavir and development of resistance. Patients taking SYMTUZA should not use products containing potent CYP3A inducers such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV. Appropriate precautions to prevent transmission should be taken.

Patients with HIV-1 harbouring mutations

SYMTUZA should not be used in experienced patients who are:

- Virologically failing and harbor any mutations associated with resistance to the antiretroviral components of SYMTUZA
- Virologically suppressed and have any known or suspected mutations associated with resistance to the antiretroviral components of SYMTUZA (see **section 5.1** Pharmacodynamic properties, Pharmacodynamic effects).

Patients co-infected with HIV and hepatitis B (HBV) or C (HCV) virus

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

The safety and efficacy of SYMTUZA in patients co-infected with HIV-1 and HBV and/or HCV have not been established.

Discontinuation of SYMTUZA therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see **section 5.1** Pharmacodynamic properties, Mechanism of action for emtricitabine and tenofovir alafenamide). Patients co-infected with HIV and HBV who discontinue SYMTUZA should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-HBV therapy may be warranted. In patients with advanced liver disease or cirrhosis, discontinuation of anti-HBV therapy is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

SYMTUZA should not be administered concomitantly with medicinal products containing tenofovir disoproxil (e.g. fumarate, phosphate, or succinate), lamivudine, or adefovir dipivoxil used for the treatment of HBV infection.

Hepatotoxicity

In patients receiving darunavir, cases of drug induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) have been reported in 0.5% of patients. Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased risk for liver function abnormalities including severe hepatic adverse events.

Appropriate laboratory testing should be conducted prior to initiating therapy with SYMTUZA and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of SYMTUZA treatment.

Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) should prompt consideration of interruption or discontinuation of SYMTUZA.

Severe skin reactions

In patients receiving darunavir, severe skin reactions may occur. These include conditions accompanied with fever and/or elevations of transaminases (reported in 0.4% of patients). Rarely (<0.1%) Stevens-Johnson Syndrome and very rarely (<0.01%) toxic epidermal necrolysis, Drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis have been reported. Discontinue SYMTUZA immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis, and/or eosinophilia.

Darunavir contains a sulfonamide moiety. SYMTUZA should be used with caution in patients with a known sulfonamide allergy. In clinical studies with darunavir/ritonavir, the incidence and severity of rash was similar in patients with or without a history of sulfonamide allergy.

Immune reconstitution inflammatory syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders such as Graves' disease and autoimmune hepatitis have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment (see **section 4.8** Adverse effects (Undesirable effects)).

Metabolic disorders

Hyperglycaemia/diabetes mellitus

New onset diabetes mellitus, hyperglycaemia, or exacerbation of existing diabetes mellitus has been reported in patients receiving antiretroviral therapy, including HIV PIs. In some of these patients the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

Consideration should be given to measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see **section 4.8** Adverse effects (Undesirable effects)).

Effects on estimated creatinine clearance

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function (see **section 5.1** Pharmacodynamic effects, Effects on serum creatinine and the Product Information for cobicistat). This effect should be considered when SYMTUZA is co-administered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance.

Nephrotoxicity

Post marketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT), and Fanconi syndrome have been reported with tenofovir alafenamide containing products; while most of these cases were characterised by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including non-steroidal anti-inflammatory drugs, are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating SYMTUZA, and during treatment with SYMTUZA on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue SYMTUZA in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

In the Phase 3 clinical trials of SYMTUZA there were no cases of proximal renal tubulopathy, including Fanconi syndrome, reported in the SYMTUZA group through Week 96.

Lactic acidosis/severe hepatomegaly with steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of SYMTUZA, and tenofovir disoproxil fumarate, another prodrug of tenofovir. Treatment with SYMTUZA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). No cases of lactic acidosis were reported in Phase 3 clinical trials.

Interactions with medicinal products

SYMTUZA can cause and/or is subject to drug interactions which may be life-threatening or result in lack of efficacy, see **section 4.3** Contraindications and **section 4.5** Interactions with other medicines and other forms of interactions.

Co-administration of SYMTUZA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see **section 4.5** Interactions with other medicines and other forms of interactions).

Use in the elderly

As limited information is available on the use of SYMTUZA in patients aged 65 and over, caution should be exercised in the administration of SYMTUZA in elderly patients, reflecting

the greater frequency of decreased hepatic function and of concomitant disease or other therapy (see **section 5.2** Pharmacokinetics, Special populations, Elderly).

Paediatric use

No dose has been established for SYMTUZA for paediatric patients 3-11 years of age or weighing less than 40 kg (see **section 5.2** Pharmacokinetic properties, Special populations). SYMTUZA should not be used in paediatric patients below 3 years of age in view of toxicity observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age (see **section 5.3** Preclinical safety data).

Effects on laboratory tests

See **section 4.8** Adverse effects (Undesirable effects).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed using SYMTUZA. Interactions that may occur with SYMTUZA are determined by interactions that have been identified with any of its components.

Darunavir and cobicistat

Darunavir is an inhibitor of CYP3A, a weak inhibitor of CYP2D6, and an inhibitor of P-glycoprotein (P-gp).

Cobicistat is an inhibitor of CYP3A and CYP2D6. Cobicistat inhibits the transporters P-gp, BCRP, MATE1, OATP1B1 and OATP1B3. Cobicistat is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is not expected to induce CYP1A2, CYP3A4, CYP2C9, CYP2C19, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), or multidrug resistance protein 1 (MDR1).

Co-administration of SYMTUZA with medicinal products primarily metabolized by CYP3A and/or CYP2D6 may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and can be associated with serious and/or life-threatening adverse events (see **section 4.3** Contraindications). Co-administration of SYMTUZA with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect.

Darunavir and cobicistat are metabolized by CYP3A. Drugs that induce CYP3A activity are expected to lower plasma concentrations of darunavir and cobicistat which may lead to loss of efficacy of darunavir and possible development of resistance (see **section 4.3** Contraindications). Co-administration of SYMTUZA and other medicinal products that inhibit CYP3A may increase plasma concentrations of darunavir and cobicistat.

SYMTUZA should not be administered concomitantly with medicinal products requiring pharmacokinetic enhancing with ritonavir or cobicistat.

Emtricitabine

Emtricitabine (FTC) is not an inhibitor of human CYP450 enzymes. *In vitro* and clinical drug interaction studies have shown that the potential for CYP-mediated interactions involving FTC with other medicinal products is low.

FTC is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug interactions due to competition for renal excretion have been observed; however, co-administration of FTC with drugs that are eliminated by active tubular secretion may

increase concentrations of FTC and/or the co-administered drug. Drugs that decrease renal function may increase concentrations of FTC.

Tenofovir alafenamide

Tenofovir alafenamide (TAF) is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*. It is not an inhibitor or inducer of CYP3A *in vivo*.

TAF is a substrate of the efflux transporter P-gp. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentrations of TAF, which may lead to loss of therapeutic effect of SYMTUZA and development of resistance. Co-administration of SYMTUZA with drugs that inhibit P-gp may increase the absorption and plasma concentration of TAF.

Expected interactions between SYMTUZA with potential concomitant drugs are listed in **Table 1** below and are based on studies conducted with the components of SYMTUZA, as individual agents or in combination, or are predicted interactions. It should be noted that the interaction profile of darunavir depends on whether ritonavir or cobicistat was used as pharmacokinetic enhancer; refer to the Product Information for darunavir for further information.

SYMTUZA is a complete antiretroviral treatment regimen. Therefore, information regarding drug interactions with other antiretroviral products is not provided.

The below list of examples of drug-drug interactions is not comprehensive and therefore the Product Information of each drug that is co-administered with SYMTUZA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Table 1: Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name Examples	**Effect on Concentration of SYMTUZA Components or Concomitant Drug**	**Clinical Comment**
α1-adrenoreceptor antagonists: alfuzosin	↑ alfuzosin	Co-administration of SYMTUZA with alfuzosin may increase alfuzosin concentrations (inhibition of CYP3A). Co-administration of SYMTUZA with alfuzosin is contraindicated.
Antacids: aluminum/magnesium, hydroxide, calcium carbonate	↔ darunavir ↔ cobicistat	SYMTUZA and antacids can be used concomitantly without dose adjustment.

Antiarrhythmics/ anti-anginals: amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine,	↑ antiarrhythmics/ anti-anginals	Co-administration of SYMTUZA with these antiarrhythmics may increase concentrations of the antiarrhythmic (inhibition of CYP3A and/or CYP2D6). Concomitant use of these antiarrhythmics and SYMTUZA is contraindicated.
dronedarone, ivabradine, ranolazine		Concomitant use of SYMTUZA with dronedarone, ivabradine or ranolazine is contraindicated.
digoxin	↑ digoxin	Co-administration of SYMTUZA with digoxin may increase concentrations of digoxin (inhibition of P-gp). The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Antibacterial: (ketolide or macrolide antibiotics) clarithromycin, erythromycin, telithromycin	effect on darunavir unknown ↑ cobicistat ↑ antibacterial	Co-administration of SYMTUZA with these antibacterials may increase concentrations of darunavir (although no darunavir increase was observed with ritonavir-boosted darunavir and clarithromycin), cobicistat, or the antibacterial (inhibition of CYP3A). SYMTUZA and clarithromycin can be used without dose adjustment in patients with normal renal function; for patients with renal impairment, consult the Product Information for clarithromycin for the recommended dosage.
Anticancer agents: dasatinib, nilotinib, vinblastine, vincristine	↑ anticancer agent	Co-administration of SYMTUZA with these anticancer agents may increase concentrations of the anticancer agent (inhibition of CYP3A), resulting in the potential for increased adverse events usually associated with these agents. Clinical monitoring is recommended when co-administering SYMTUZA with these anticancer agents.
everolimus, irinotecan		Concomitant use of everolimus or irinotecan and SYMTUZA is not recommended.

Anticoagulants: Direct Oral Anticoagulants (DOACs):	↑ DOACs	DOACs are primarily metabolized by CYP3A4 and/or transported by P-gp. Co-administration with SYMTUZA may result in increased plasma concentrations of the DOAC, which may lead to an increased bleeding risk.
apixaban, rivaroxaban		Co-administration of a DOAC affected by both P-gp and CYP3A4, including rivaroxaban, is not recommended with SYMTUZA. Co-administration of apixaban with SYMTUZA is contraindicated.
dabigatran etexilate, edoxaban	↑ dabigatran	The results of a drug-drug interaction study between darunavir/cobicistat 800/150 mg and dabigatran etexilate 150 mg in healthy participants showed a 2.6-fold increase in dabigatran plasma AUC after single dosing of darunavir/cobicistat, and a 1.9-fold increase in dabigatran plasma AUC after repeated dosing of darunavir/cobicistat. The study demonstrated a 2.6-fold increase in dabigatran plasma Cmax after single dosing of darunavir/cobicistat and a 2.0-fold increase in dabigatran plasma Cmax after repeated dosing of darunavir/cobicistat. Clinical monitoring is required when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate and edoxaban, is co-administered with SYMTUZA. A dose reduction of the DOAC may be needed.
warfarin	effect on warfarin unknown	Co-administration of SYMTUZA with warfarin may affect warfarin concentrations. When SYMTUZA is co-administered with warfarin, the international normalized ratio (INR) should be monitored and used for titration of warfarin dose to obtain the desired clinical effect.

Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ darunavir ↓ cobicistat ↓ tenofovir alafenamide	Co-administration of SYMTUZA with carbamazepine, phenobarbital, or phenytoin (which are CYP3A and P-gp inducers) decreases plasma concentrations of darunavir, cobicistat, and tenofovir alafenamide which may result in loss of therapeutic effect and development of resistance. Concomitant use of SYMTUZA with these anticonvulsants is contraindicated.
oxcarbazepine		Co-administration of SYMTUZA with oxcarbazepine may decrease darunavir, cobicistat, and/or tenofovir alafenamide concentrations (induction of CYP3A and P-gp), which may result in loss of therapeutic effect and development of resistance. Co-administration of SYMTUZA with oxcarbazepine is not recommended. Alternative anticonvulsants should be considered.
clonazepam	↑clonazepam	Co-administration of SYMTUZA with clonazepam may increase concentrations of the anticonvulsant (inhibition of CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA with this anticonvulsant.
Antidepressants: amitriptyline, desipramine, imipramine, paroxetine, nortriptyline, sertraline, trazodone	↑ antidepressant	Concomitant use of SYMTUZA and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA with these antidepressants and a dose adjustment of the antidepressant may be needed.
Antiemetics: domperidone	↑ domperidone	Use with caution: monitor for domperidone adverse reactions.
Antifungals: itraconazole, isavuconazole, clotrimazole, fluconazole, ketoconazole,	↑ darunavir ↑ cobicistat ↑ tenofovir alafenamide ↑ antifungal	Co-administration of SYMTUZA with these antifungals may increase concentrations of darunavir, cobicistat, tenofovir alafenamide, and/or the antifungal (inhibition of CYP3A and/or P-gp). Clinical monitoring is recommended when co-administering SYMTUZA with these antifungals. When used in combination with SYMTUZA, the dose of itraconazole or ketoconazole should not exceed 200 mg per day.
posaconazole,		Clinical monitoring is recommended when co-administering SYMTUZA with posaconazole.
voriconazole		Concentrations of voriconazole may increase or decrease when co-administered with SYMTUZA. Voriconazole should not be administered to patients receiving SYMTUZA unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

Antihistamines: astemizole, terfenadine	↑ antihistamines	Exposure to these antihistamines may be increased when co-administered with SYMTUZA. Concomitant use of SYMTUZA with astemizole and terfenadine is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. .
Anti-gout: colchicine	↑ colchicine	Concomitant use of SYMTUZA with colchicine may increase concentrations of colchicine (inhibition of CYP3A). Refer to colchicine Product Information for dosing recommendations. Co-administration of SYMTUZA with colchicine is contraindicated in patients with renal or hepatic impairment.
Antimalarial: artemether/ lumefantrine	↔ darunavir ↑ artemether ↑ lumefantrine	Co-administration of SYMTUZA with artemether/ lumefantrine may increase concentrations of artemether and lumefantrine (inhibition of CYP3A). The combination of SYMTUZA and artemether/ lumefantrine can be used without dose adjustments; however, due to the expected increase in lumefantrine exposure, the combination should be used with caution.
Antimycobacterial: rifabutin, rifampin, rifapentine	↓ darunavir ↓ cobicistat ↓ tenofovir alafenamide ↑ rifabutin	Co-administration of SYMTUZA with rifabutin, rifampin, or rifapentine may decrease darunavir, cobicistat, and/or tenofovir alafenamide concentrations (induction of CYP3A and P-gp), which may result in loss of therapeutic effect and development of resistance. Rifabutin concentrations may be increased when co-administered with SYMTUZA. Co-administration of SYMTUZA with rifapentine is not recommended. Unlike ritonavir-boosted darunavir regimens, co-administration of SYMTUZA with rifabutin is not recommended. If combination of rifabutin and SYMTUZA is required, the recommended dose of rifabutin is 150 mg every other day. Clinical monitoring is recommended when co-administering SYMTUZA with rifabutin. Co-administration of SYMTUZA with rifampin is contraindicated.
Antiplatelets: clopidogrel	↓ clopidogrel active metabolite	Co-administration of SYMTUZA with clopidogrel is expected to decrease clopidogrel active metabolite plasma concentration, which may reduce the antiplatelet activity of clopidogrel. Co-administration of SYMTUZA with clopidogrel is not recommended.
prasugrel	↔prasugrel active metabolite	SYMTUZA is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel.

β-blockers: carvedilol, metoprolol, timolol	↑ beta-blockers	Co-administration of SYMTUZA and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when co-administering SYMTUZA with beta-blockers and a lower dose of the beta-blocker should be considered.
Calcium channel blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blockers	Co-administration of SYMTUZA with calcium channel blockers may increase concentrations of the calcium channel blocker (inhibition of CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA with calcium channel blockers.
Contraceptives: drospirenone, ethinylestradiol, norethindrone	↑ drospirenone ↓ ethinylestradiol ↓ norethindrone (based on theoretical considerations)	When SYMTUZA is co-administered with a drospirenone-containing product, clinical monitoring is recommended due to the potential for hyperkalemia. No data are available to make recommendations on the use of SYMTUZA with other hormonal contraceptives. Therefore, additional or alternative (non-hormonal) methods of contraception are recommended.
Corticosteroid: dexamethasone (systemic)	↓ darunavir ↓ cobicistat	Co-administration of SYMTUZA with systemic dexamethasone may decrease darunavir and/or cobicistat concentrations (induction of CYP3A) which may result in loss of therapeutic effect of and development of resistance. Co-administration of SYMTUZA with (systemic) dexamethasone is not recommended.
Corticosteroids primarily metabolised by CYP3A: betamethasone, budesonide, fluticasone, mometasone, prednisone, triamcinolone	↑ corticosteroid	Corticosteroid concentrations may be increased when co-administered with SYMTUZA. Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when co-administering SYMTUZA with corticosteroids. Alternatives should be considered, particularly for long-term use. For co-administration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.

Endothelin receptor antagonists: bosentan	↓ darunavir ↓ cobicistat ↑ bosentan	Bosentan concentrations may be increased when co-administered with SYMTUZA. Clinical monitoring is recommended when co-administering SYMTUZA with bosentan and a dose adjustment of bosentan may be needed. Co-administration of bosentan with SYMTUZA may lead to decreased cobicistat plasma concentrations and consequently that of darunavir, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended.
Ergot alkaloids: ergotamine, ergonovine, dihydroergotamine, methylergonovine	↑ ergot alkaloids	Exposure to the ergot alkaloids may be increased when co-administered with SYMTUZA. Concomitant use of SYMTUZA with ergot alkaloids is contraindicated.
Eugeroics: armodafinil, modafinil	↓ darunavir ↓ cobicistat	Co-administration of SYMTUZA with armodafinil or modafinil may decrease darunavir and/or cobicistat concentrations (induction of CYP3A), which may result in loss of therapeutic effect and development of resistance. Co-administration of SYMTUZA and armodafinil or modafinil is not recommended.
GI motility agents: cisapride	↑ cisapride	Exposure to cisapride may be increased when co-administered with SYMTUZA. Concomitant use of SYMTUZA with cisapride is contraindicated.
H2-receptor antagonists: cimetidine, famotidine, nizatidine, ranitidine	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (i.e. decreased gastric acidity) no interaction is expected when SYMTUZA is co-administered with H2-receptor antagonists. SYMTUZA can be co-administered with H2-receptor antagonists without dose adjustment.

Hepatitis C Virus (HCV) direct-acting agents: boceprevir	↓ darunavir ↓ boceprevir	Concomitant administration of SYMTUZA with boceprevir may decrease darunavir and/or boceprevir concentrations (mechanism unknown) and has the potential to adversely affect the intracellular activation and antiviral efficacy of tenofovir alafenamide based on in vitro data. Co-administration of SYMTUZA with boceprevir is not recommended.
elbasvir/grazoprevir	↑ grazoprevir	Concomitant use of elbasvir/grazoprevir and SYMTUZA may increase the exposure to grazoprevir (inhibition of OATP1B and CYP3A). Concomitant use of SYMTUZA with elbasvir/grazoprevir is contraindicated.
glecaprevir/pibrentasvir	↑ glecaprevir ↑ pibrentasvir	Concomitant use of glecaprevir/pibrentasvir and SYMTUZA may increase the exposure to glecaprevir and pibrentasvir (inhibition of P-gp, BCRP and/or OATP1B1/3). Co-administration of SYMTUZA with glecaprevir/pibrentasvir is not recommended.
sofosbuvir, ledipasvir, daclatasvir		Based on mechanistic considerations, no clinically relevant interaction is expected when SYMTUZA is co-administered with sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir. SYMTUZA can be co-administered with sofosbuvir, sofosbuvir/ledipasvir, or daclatasvir without dose adjustment.
Herbal products: St. John's wort	↓ darunavir ↓ cobicistat ↓ tenofovir alafenamide	Co-administration of SYMTUZA with products containing St. John's wort (Hypericum perforatum) may cause significant decreases in darunavir, cobicistat, and/or tenofovir alafenamide concentrations (induction of CYP3A or P-gp), which may result in loss of therapeutic effect and development of resistance. Co-administration of SYMTUZA with products containing St. John's wort (Hypericum perforatum) is contraindicated.
HMG-CoA reductase inhibitors: atorvastatin, pitavastatin, pravastatin, rosuvastatin,	↑ HMG-CoA reductase inhibitors	Concomitant use of a HMG-CoA reductase inhibitor and SYMTUZA may increase plasma concentrations of the lipid lowering agent (inhibition of CYP3A and/or transport), which may lead to adverse events such as myopathy. Clinical monitoring is recommended when co-administering SYMTUZA with HMG-CoA reductase inhibitors and a lower dose of the lipid lowering agent should be considered. When administration of atorvastatin and SYMTUZA is desired, it is recommended to start with an atorvastatin dose of 10 mg q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response.
lovastatin, simvastatin		Co-administration of SYMTUZA with lovastatin or simvastatin is contraindicated.

Other lipid modifying agents: lomitapide	↑ lomitapide	SYMTUZA is expected to increase the exposure of lomitapide when co-administered. Co-administration is contraindicated.
Immunosuppressants: cyclosporine, everolimus, sirolimus, tacrolimus	↑ immunosuppressants	Co-administration of SYMTUZA and these immunosuppressants may increase concentrations of the immunosuppressants (inhibition of CYP3A). Co-administration of cyclosporine is expected to increase plasma concentrations of tenofovir alafenamide (P-gp inhibition). Combination of SYMTUZA with these immunosuppressants should be used with caution. Therapeutic concentration monitoring is recommended for the immunosuppressant when co-administered with SYMTUZA. Concomitant use of everolimus and SYMTUZA is not recommended.
Inhaled beta agonist: salmeterol	↑ salmeterol	Co-administration of SYMTUZA with salmeterol may increase concentrations of salmeterol (inhibition of CYP3A). The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia. Co-administration of SYMTUZA with salmeterol is not recommended.
Narcotic analgesics: fentanyl, oxycodone, tramadol	↑ analgesic	Co-administration of SYMTUZA with these analgesics may increase concentrations of the analgesic (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA with these analgesics.
Narcotic analgesic/ treatment of opioid dependence: buprenorphine, buprenorphine/ naloxone, naloxone, methadone	↔ buprenorphine ↑ norbuprenorphine ↔ naloxone ↓ methadone	No a priori dose adjustment of buprenorphine or methadone is required when co-administering with SYMTUZA. However, careful clinical monitoring is recommended as the dose of buprenorphine or methadone may need to be adjusted in some patients.
Neuroleptics/ antipsychotics: Lurasidone, perphenazine, pimozide, risperidone, thioridazine	↑ neuroleptics	Co-administration of SYMTUZA and these neuroleptics may increase concentrations of the neuroleptic (inhibition of CYP3A or CYP2D6). Clinical monitoring is recommended when co-administering SYMTUZA with these neuroleptics and a lower dose of the neuroleptic should be considered. Co-administration of SYMTUZA with lurasidone and pimozide is contraindicated.
quetiapine	↑ quetiapine	Concomitant use of quetiapine and SYMTUZA may increase the exposure to quetiapine (inhibition of CYP3A). Initiation of SYMTUZA in patients taking quetiapine:

		consider alternative antiretroviral therapy to avoid increases in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine Product Information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking SYMTUZA: refer to the quetiapine Product Information for initial dosing and titration of quetiapine.
Opioid antagonist: naloxegol	↑ naloxegol	Co-administration of SYMTUZA and naloxegol is contraindicated.
Phosphodiesterase PDE-5 inhibitors: avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors	Co-administration of SYMTUZA and PDE-5 inhibitors may increase concentrations of the PDE-5 inhibitor (inhibition of CYP3A), which may lead to adverse events such as hypotension, syncope, visual disturbances and priapism. Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH): • Co-administration of SYMTUZA with sildenafil is contraindicated (see **section 4.3** Contraindications). • The following dose adjustments are recommended for use of tadalafil with SYMTUZA: Co-administration of tadalafil in patients on SYMTUZA: In patients receiving SYMTUZA for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Co-administration of SYMTUZA in patients on tadalafil: Avoid use of tadalafil during the initiation of SYMTUZA. Stop tadalafil at least 24 hours prior to starting SYMTUZA. After at least one week following the initiation of SYMTUZA, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse events. Co-administration of SYMTUZA and avanafil is not recommended.

Platelet aggregation inhibitors: ticagrelor	↑ ticagrelor	Co-administration of SYMTUZA with ticagrelor may increase concentrations of ticagrelor (inhibition of CYP3A and/or P-gp). Co-administration of SYMTUZA and ticagrelor is not recommended.
Proton pump inhibitors: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	↔ darunavir ↔ cobicistat	SYMTUZA and proton pump inhibitors can be co-administered without dose adjustment.
Sedatives/hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, parenterally administered midazolam, zolpidem	↑ sedatives/hypnotics	Co-administration of SYMTUZA with these sedatives/hypnotics may increase concentrations of the benzodiazepine (inhibition of CYP3A). Clinical monitoring is recommended when co-administering SYMTUZA with these sedatives/ hypnotics and a lower dose of the sedatives/hypnotics should be considered. Co-administration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered.
oral midazolam, triazolam		Co-administration of SYMTUZA with oral midazolam or triazolam is contraindicated.
Treatment of premature ejaculation: dapoxetine	↑ dapoxetine	Co-administration with SYMTUZA with dapoxetine is contraindicated.
Urinary antispasmodics: fesoterodine solifenacin	↑ urinary antispasmodics	Use with caution. Monitor for fesoterodine or solifenacin adverse reactions. Dose reduction of fesoterodine or solifenacin may be necessary.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No reproductive toxicity studies have been conducted with darunavir, cobicistat, emtricitabine and tenofovir alafenamide in combination.

Darunavir: In a study conducted in rats, there were no effects on mating or fertility with DRV treatment up to 1000 mg/kg/day and exposure levels below (AUC 0.6-fold) of that in human at the clinically recommended dose.

Cobicistat: Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4-fold higher than human exposures at the recommended 150 mg daily dose. Fertility was normal in the offspring of rats exposed daily from before birth (*in utero*) through sexual

maturity at daily exposures (AUC) of approximately 1.7-fold higher than human exposures at the recommended 150 mg daily dose.

Emtricitabine: Reproductive studies were conducted in rats, mice, and rabbits. Animal studies did not indicate harmful effects of FTC with respect to fertility, pregnancy, fetal parameters, parturition, or postnatal development. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 40 times higher than human exposures at the recommended 200 mg daily dose.

Tenofovir alafenamide: There were no effects on fertility, mating performance or early embryonic development when tenofovir alafenamide was administered to male rats at a dose up to 160 mg/kg/day, equivalent to 155 times the human dose based on body surface area comparisons, for 28 days prior to mating and to female rats for 14 days prior to mating through day seven of gestation.

Use in pregnancy

Category B2

There are no human data on the use of SYMTUZA during pregnancy. Darunavir/cobicistat (800/150 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 7 pregnant women during the second and third trimesters, and postpartum (6-12 weeks). The pharmacokinetic data demonstrate that exposure to darunavir and cobicistat was substantially lower during pregnancy compared with postpartum (see **section 5.2** Pharmacokinetic properties, Special populations, Pregnancy and postpartum). Virologic response was sustained throughout the study period in 5 out of 6 women who completed the study; the subject with virologic failure was not compliant with study medication. No pharmacokinetic data are available for emtricitabine and tenofovir alafenamide during pregnancy.

Therapy with SYMTUZA should not be initiated during pregnancy, and women who become pregnant during therapy with SYMTUZA should be switched to an alternative regimen (see **section 4.2** Dosage and method of administration, Dosage adjustment, Pregnancy and postpartum). Darunavir/ritonavir in combination with emtricitabine/tenofovir alafenamide may be considered as an alternative.

At clinically relevant exposures, animal studies with SYMTUZA components do not indicate developmental or reproductive toxicity (see **section 5.3** Preclinical safety data, Toxicology, Reproductive toxicology).

Darunavir: In a study conducted in rats with DRV Treatment up to 1000 mg/kg/day and exposure levels below (AUC 0.6-fold) of that in human at the clinically recommended dose, there was no teratogenicity with DRV in rats and rabbits when treated alone, nor in mice when treated in combination with ritonavir. The exposure levels were lower than those with the recommended clinical dose in humans. In addition, rats treated with combination with ritonavir showed no teratogenicity with the increase in exposure levels which are higher than those with the recommended clinical dose in humans.

Cobicistat: Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 1.7 and 4.1 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Emtricitabine: No evidence of embryofoetal toxicity or teratogenicity was observed in mice or rabbits at respective emtricitabine exposures (AUC) of 40- and 7.3-fold the clinical exposure. Impaired weight gain observed in pregnant rabbits at doses resulting in emtricitabine exposures (AUC) at least 26 times the clinical exposure was not associated with any adverse foetal effects.

Tenofovir alafenamide: Embryo-foetal development studies have been performed in rats and rabbits which revealed no evidence of embryolethality, foetotoxicity or teratogenicity due to tenofovir alafenamide. The embryo-foetal NOAELs in rats and rabbits occurred at TAF exposures (AUC) similar to and 85 times higher than, respectively, the exposure in humans at the recommended daily dose.

Use in lactation

Emtricitabine is excreted in human milk. It is not known whether darunavir, cobicistat, or tenofovir alafenamide are excreted in human milk. Animal studies have demonstrated that darunavir, cobicistat, and tenofovir are excreted in milk.

There is insufficient information on the effects of cobicistat, emtricitabine, and tenofovir in newborns/infants, and children below 3 years of age should not be exposed to darunavir (see **section 5.3** Preclinical safety data, Toxicology, Juvenile toxicity). Therefore, SYMTUZA should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant, HIV infected women should be instructed not to breast-feed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of SYMTUZA or its components on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of darunavir/cobicistat/ emtricitabine/tenofovir alafenamide based on the comprehensive assessment of the available information. A causal relationship with darunavir/cobicistat/emtricitabine/tenofovir alafenamide cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The overall safety profile of SYMTUZA is based on the Week 48 data from two randomized, comparative Phase 3 trials, TMC114FD2HTX3001 (AMBER) and TMC114 IFD3013 (EMERALD), and on all available clinical trial and post-marketing data of its components. The Week 96 safety profile of SYMTUZA is consistent with the Week 48 SYMTUZA safety profile. As SYMTUZA contains darunavir, cobicistat, emtricitabine, and tenofovir alafenamide, the adverse reactions associated with each of the individual compounds may be expected.

Adverse reactions in treatment-naïve adults

The safety profile of SYMTUZA in treatment-naïve HIV-1 infected adults is based on Week 48 data from a randomized, double-blind, active-controlled trial TMC114FD2HTX3001 (AMBER) where a total of 362 subjects received SYMTUZA once daily and 363 subjects received a combination of fixed-dose combination of darunavir and cobicistat and fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate (F/TDF). Adverse reactions (≥Grade 2 severity) reported in AMBER are shown in Table 2.

The median exposure in patients treated with SYMTUZA was 96.1 weeks. The majority of the adverse reactions reported during treatment with SYMTUZA were mild in severity. The most frequent (≥2%) adverse reactions (≥Grade 2 severity) to SYMTUZA were diarrhea, rash and headache. No Grade 4 adverse reactions were reported. 2.2% of the patients discontinued treatment due to adverse reactions.

Table 2: Adverse Reactions (≥Grade 2 Severity) Reported in SYMTUZA treated HIV-1 Infected Treatment-Naïve Adults in AMBER

	Week 48		Week 96*
System Organ Class Adverse Reaction	**SYMTUZA (N=362)**	**D/C + F/TDF (N=363)**	**SYMTUZA (N=362)**
Gastrointestinal disorders			
Diarrhea	3.9%	5.0%	5.5%
Dyspepsia	1.1%	0.8%	1.1%
Nausea	0.8%	3.6%	0.8%
Vomiting	0.8%	1.7%	0.8%
Abdominal pain	0.6%	0.8%	0.8%
Flatulence	0.3%	0	0.3%
Skin and subcutaneous tissue disorders			
Rash	4.4%	4.4%	5.0%
Pruritus	0.6%	0.6%	0.8%
Angioedema	0.3%	0	0.3%
Nervous system disorders			
Headache	1.9%	3.0%	2.8%
General disorders and administration site conditions			
Fatigue	1.4%	1.7%	1.9%
Asthenia	0	0.3%	0.3%
Musculoskeletal and connective tissue disorders			
Myalgia	0.6%	0.6%	0.8%
Psychiatric disorders			
Abnormal dreams	0	0.6%	0.3%

* Period baseline to Week 96. No comparator data available beyond Week 48

Laboratory abnormalities (≥Grade 2 severity), reported in AMBER and considered adverse reactions are shown in **Table 3**.

Table 3: Laboratory Abnormalities, Grade 2-4, observed in SYMTUZA Treated Patients, Considered Adverse Reactions in AMBER

		Week 48		Week 96****
Laboratory Parameter Grade	**Limit**	**SYMTUZA N=362 %***	**D/C + F/TDF N=363 %***	**SYMTUZA N=362 %***
Amylase				
Grade 2	1.5 to < 3.0x ULN	1.9%	4.7%	2.5%
Grade 4	≥5.0x ULN	0.3%	0	0.3%
Lipase**				
Grade 2	>1.5 to <3.0 x ULN	0.3%	1.1%	0.8%
Grade 3	3.0 to <5.0 x ULN	0	0.6%	0.3%

Laboratory Parameter Grade	Limit	Week 48 SYMTUZA N=362 %*	Week 48 D/C + F/TDF N=363 %*	Week 96**** SYMTUZA N=362 %*
Creatinine				
Grade 2	>1.3 to 1.8 x ULN OR Increase of >0.3 mg/dL above baseline	4.1%	13.7%	7.7%
Grade 4	≥3.5x ULN OR Increase of ≥2.0x above baseline	0.3	0	0.3%
Triglycerides, fasting				
Grade 2	>3.42 to 5.7 mmol/L	6.6%	3.6%	11.6%
Grade 3	>5.7 to ≤11.4 mmol/L	0.8%	0.8%	3%
Grade 4***	>11.4 mmol/L	0.3%	0.3%	0.8%
Total Cholesterol, fasting				
Grade 2	6.19 to <7.7 mmol/L	17.1%	1.1%	28.5%
Grade 3	≥7.7 mmol/L	1.7%	0.6%	3.9%
LDL Cholesterol, fasting				
Grade 2	4.12 to <4.90 mol/L	8.6%	3.6%	18.5%
Grade 3	≥4.90 mol/L	4.7%	1.1%	8.3%
Hyperglycemia				
Grade 2	6.95 to <13.89 mmol/L	6.4%	5.5%	9.4%
Grade 3	13.89 to <27.75 mmol/L	0.3%	0	0.3%
Alanine Aminotransferase				
Grade 2	>2.5 to <5.0 x ULN	0.3%	1.7%	0.8%
Grade 3	≥5.0 to <10.0 x ULN	1.1%	0.6%	1.7%
Grade 4	≥10.0x ULN	0.3%	0.3%	1.1%
Aspartate Aminotransferase				
Grade 2	>2.5 to <5.0 x ULN	0.8%	1.1%	2.8%
Grade 3	>5.0 to <10.0 x ULN	1.1%	1.1%	1.1%
Grade 4	≥10.0x ULN	0	0.6%	0.8%

Note: no Grade 2-4 abnormalities were reported for Alkaline Phosphatase
N=total number of subjects in the intent-to-treat (ITT) population
* The number of subjects with data can vary per laboratory parameter, but the denominator to calculate is the ITT population.
** Reflex lipase testing was performed only when total amylase >1.5x ULN.
*** Note: as the grading scale for some parameters in the DAIDS (Division of Acquired Immunodeficiency Syndrome) grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones will be allocated to the adjacent worst-case grade.
**** Period baseline to Week 96. No comparator data available beyond Week 48.

Adverse reactions in virologically-suppressed adults

The safety profile of SYMTUZA in virologically-suppressed HIV-1 infected adults is based on Week 48 data from 1141 subjects in a randomized, open-label, active-controlled trial, TMC114IFD3013 (EMERALD), in which 763 subjects with a stable antiretroviral regimen consisting of a boosted protease inhibitor [either darunavir once daily or atazanavir (both boosted with ritonavir or cobicistat), or lopinavir with ritonavir] combined with emtricitabine and tenofovir disoproxil fumarate switched to SYMTUZA, and 378 subjects continued their treatment regimen of a boosted protease inhibitor with emtricitabine and tenofovir disoproxil fumarate. Overall, the safety profile of SYMTUZA in subjects in this study was similar to that in treatment naïve-subjects. The median exposure in patients treated with SYMTUZA was 96.1 weeks. The most frequent (≥2%) adverse reactions (≥Grade 2 severity) to SYMTUZA were diarrhea, headache, and abdominal pain. One Grade 4 adverse reaction was reported (diabetes mellitus). The proportion of subjects who

discontinued treatment with SYMTUZA due to adverse reactions, regardless of severity, was 0.5%. Adverse reactions (≥Grade 2 severity) reported in EMERALD are shown in Table 4.

Table 4: Adverse Reactions (≥Grade 2 Severity) in SYMTUZA Treated HIV-1 Infected, Virologically Suppressed Subjects Switching From a Boosted PI+F/TDF Regimen to SYMTUZA (EMERALD)

	Week 48		Week 96*
System Organ Class Adverse Reaction	**SYMTUZA (N=763)**	**bPI+F/TDF (N=378)**	**SYMTUZA (N=763)**
Gastrointestinal disorders			
Diarrhea	2.5%	2.1%	3.9%
Abdominal pain	2.0%	1.1%	3.1%
Nausea	0.5%	0.8%	0.9%
Dyspepsia	0.4%	0.3%	0.8%
Vomiting	0.4%	0.5%	0.8%
Abdominal distension	0.3%	0	0.4%
Pancreatitis acute	0.1%	0	0.3%
Flatulence	0	0	0.1%
Nervous system disorders			
Headache	2.4%	0.3%	3.5%
Skin and subcutaneous tissue disorders			
Angioedema	0.5%	0.5%	0.5%
Pruritus	0.3%	0	0.3%
Rash	0.3%	0.3%	0.8%
Urticaria	0.3%	0	0.3%
General disorders and administration site conditions			
Fatigue	0.9%	1.1%	1.6%
Metabolism and nutrition disorders			
Diabetes mellitus	0.8%	0	1.2%
Anorexia	0	0.3%	0.1%
Musculoskeletal and connective tissue disorders			
Myalgia	0.5%	0.5%	0.8%
Osteonecrosis	0.1%	0	0.4%
Psychiatric disorders			
Abnormal dreams	0.4%	0	0.4%
Immune system disorders			
(Drug) hypersensitivity	0.1%	0.3%	0.5%

* Period baseline to Week 96. No comparator data available beyond Week 48.

Laboratory abnormalities (≥Grade 2 severity), reported in EMERALD and considered adverse reactions are shown in Table 5.

Table 5: Laboratory Abnormalities, Grade 2-4, Considered Adverse Reactions in EMERALD

		Week 48		Week 96****
Laboratory Parameter Grade	**Limit**	**SYMTUZA N=763 %***	**bPI+F/TDF N=378 %***	**SYMTUZA N=763 %***
Amylase				
Grade 2	1.5 to < 3.0x ULN	4.2%	6.9%	5.1%
Grade 3	3.0 to <5.0x ULN	0.4%	0.3%	0.4%
Grade 4	≥5.0x ULN	0.1%	0.3%	0.3%
**Lipase ** **				
Grade 2	1.5 to <3.0x ULN	0.4%	1,1%	0.4%
Grade 3	3.0 to <5.0x ULN	0.4%	0	0.7%
Grade 4	≥5.0x ULN	0.3%	0.5%	0.3%
Creatinine				
Grade 2	>1.3 to 1.8x ULN OR Increase of >0.3 mg/dL above baseline	5.4%	6.3%	8.8%
Grade 3	>1.8 to <3.5x ULN OR Increase of 1.5 to <2.0x above baseline	0.3%	0.3%	0.4%
Triglycerides, fasting				
Grade 2	>3.42 to 5.7 mmol/L	5.4%	6.1%	6.7%
Grade 3	>5.7 to ≤11.4 mmol/L	1.4%	2.1%	2.2%
Grade 4***	>11.4 mmol/L	0.4%	0	0.8%
Total Cholesterol, fasting				
Grade 2	6.19 to <7.77 mmol/L	21%	4.5%	25.2%
Grade 3	≥7.77 mmol/L	3.7%	1.6%	4.7%
LDL Cholesterol, fasting				
Grade 2	4.12 to <4.90 mmol/L	15.6%	4.5%	19.1%
Grade 3	≥4.90 mmol/L	6.3%	1.6%	8.8%
Hyperglycemia				
Grade 2	6.95 to <13.89 mmol/L	6.9%	5.6%	8.0%
Grade 3	13.89 to <27.75 mmol/L	1.0%	0.5%	1.4%
Alanine Aminotransferase				
Grade 2	2.5 to <5.0 x ULN	18 (2.4%)	5 (1.3%)	22 (2.9%)
Grade 3	≥5.0 to <10.0 x ULN	5 (0.7%)	4 (1.1%)	6 (0.8%)
Grade 4	≥10.0x ULN	3 (0.4%)	5 (1.3%)	6 (0.8%)
Aspartate Aminotransferase				
Grade 2	2.5 to <5.0 x ULN	1.6%	1.6%	2.6%
Grade 3	≥5.0 to <10.0 x ULN	0.9%	1.6%	1.3%
Grade 4	≥10.0x ULN	0.5%	1.1%	0.8%
Alkaline phosphatase				
Grade 2	2.5 to <5.0x ULN	0.3%	0	0.5%

N=total number of subjects in the ITT population

* The number of subjects with data can vary per laboratory parameter, but the denominator to calculate percentage is the ITT population .

** Reflex lipase testing was performed only when total amylase >1.5x ULN.

*** Note: as the grading scale for some parameters in the DAIDS grading table has some gaps (zones where no toxicity grade definition exists), laboratory results falling in these zones will be allocated to the adjacent worst-case grade.

**** Period baseline to Week 96. No comparator data available beyond Week 48.

The following additional Adverse Reactions have been observed in darunavir trials:

Hepatobiliary disorders: acute hepatitis
Immune system disorders: Immune reconstitution inflammatory syndrome
Reproductive system and breast disorders: gynecomastia
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Post-marketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported for SYMTUZA components during post-marketing experience (**Table 6**). Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), and very rare (<1/10000, including isolated reports). See **section 4.4** Special warnings and precautions for use.

Table 6: Adverse Reactions Identified During Post-Marketing Experience

System Organ Class	Adverse Reaction	Frequency Category Estimated from Spontaneous Reporting Rates
Skin and subcutaneous tissue disorders*	Acute generalized exanthematous pustulosis	Very rare
	Drug reaction with eosinophilia and systemic symptoms (DRESS)	Very rare
	Toxic epidermal necrolysis	Very rare
Renal and Urinary Disorders	Acute renal failure	Unknown
	Proximal renal tubulopathy	Unknown
	Fanconi syndrome	Unknown
	Crystal nephropathy	Very rare

* Postmarketing spontaneous reporting rates were based on estimated exposure of person-years of DRV/rtv and DRV/COBI treatment

Description of selected adverse reactions

Rash

Rash is a common adverse reaction in patients treated with darunavir. Rash was mostly mild to moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. In the Phase 3 trial investigating SYMTUZA as a single tablet regimen in treatment-naïve patients, 13% of patients receiving SYMTUZA (N=362) experienced rash (most of which were grade 1), of which 1.7% of patients discontinued treatment due to rash.

Decrease estimated creatinine clearance

Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function as assessed, for instance, by using Cystatin C (Cyst C) as filtration marker.

In the Phase 3 trial of SYMTUZA in treatment-naïve patients, increases in serum creatinine and decreases in $eGFR_{CG}$ occurred at the first on-treatment assessment (Week 2) and remained stable through 96 weeks. At Week 48, changes from baseline were smaller with darunavir/ cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) than with darunavir+cobicistat+ emtricitabine/tenofovir disoproxil fumarate (D+C+F/TDF). The median change in $eGFR_{CG}$

was -5.5 mL/min with D/C/F/TAF and -12 mL/min with D/C+F/TDF (p=<0.001). Using Cyst C as filtration marker, the median changes in estimated glomerular filtration rate calculated using the CKD-EPI ($eGFR_{CKD\text{-}EPI}$ Cyst C) formula were respectively 4.0 mL/min/1.73 m² and 1.6 mL/min/1.73 m² (p=0.001). At Week 96, the median change in $eGFR_{CG}$ was -5.2 mL/min with D/C/F/TAF. Using Cyst C as filtration marker, the median change in estimated glomerular filtration rate calculated using the CKD-EPI ($eGFR_{CKD\text{-}EPI\ Cyst\ C}$) formula (N=22) was +4.4 mL/min/1.73 m² with D/C/F/TAF.

Special populations

Paediatric patients

The safety of SYMTUZA in paediatric patients has not been investigated. However, the safety of SYMTUZA components was evaluated through the clinical studies TMC114-C230 (N=12) for darunavir with ritonavir and GS-US-292-0106 (N=50) for a fixed-dose combination containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide. Data from these studies showed that the overall safety profile in adolescent patients aged 12 to <18 years and weighing at least 40 kg was similar to that observed in the adult population.

Patients co-infected with hepatitis B and/or hepatitis C virus

Limited information is available on the use of SYMTUZA components in patients co-infected with hepatitis B and/or C virus. In co-infected patients receiving darunavir/ritonavir, the incidence of adverse events and clinical chemistry abnormalities was not higher than in patients who were not co-infected, except for increased hepatic enzymes. The pharmacokinetic exposure in co-infected patients was comparable to that in patients without co-infection. The safety of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet was evaluated in approximately 70 HIV/HBV co-infected patients receiving treatment for HIV in an open-label clinical study (GS-US-292-1249). Based on this limited experience, the safety profile of emtricitabine and tenofovir alafenamide in patients with HIV/HBV co-infection appears to be similar to that in patients with HIV-1 monoinfection.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Human experience of acute overdose with SYMTUZA is limited. If overdose occurs, the patient must be monitored for evidence of toxicity (see **section 4.8** Adverse Effects (Undesirable effects)).

There is no specific antidote for overdose with SYMTUZA. Treatment of overdose with SYMTUZA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

Since darunavir and cobicistat are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Emtricitabine can be removed by hemodialysis, which removes approximately 30% of the dose over a 3 hour dialysis period starting within 1.5 hours of emtricitabine dosing. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

For further information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antivirals for systemic use, Antivirals for treatment of HIV infection, Combinations - ATC code: J05AR22.

Mechanism of action

SYMTUZA consists of the HIV protease inhibitor darunavir (DRV), the pharmacokinetic enhancer cobicistat (COBI), the nucleoside reverse transcriptase inhibitor emtricitabine (FTC), and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF).

Darunavir: DRV is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. DRV tightly binds to the HIV-1 protease with a K_D of 4.5 × 10^{-12} M. DRV shows resilience to the effects of HIV protease inhibitors resistance-associated mutations. DRV is not an inhibitor of any of 13 tested human cellular proteases.

Cobicistat: Cobicistat is a mechanism-based inhibitor of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such as DRV, where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism.

Emtricitabine: FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. FTC has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus. FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Tenofovir alafenamide: TAF is a phosphonamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in concentrating tenofovir in peripheral blood mononuclear cells (PBMCs) or HIV target cells including lymphocytes and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. Tenofovir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus. *In vitro* studies have shown that both FTC and tenofovir can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity *in vitro* based on several assays including mitochondrial DNA analyses.

Pharmacodynamic effects

Microbiology

Antiviral activity *in vitro*

Darunavir: DRV exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human PBMCs, and human

monocytes/macrophages with median EC_{50} (50% effective concentration) values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). DRV demonstrates antiviral activity *in vitro* against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from <0.1 to 4.3 nM. These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to >100 µM. The EC_{50} value of DRV increases by a median factor of 5.4 in the presence of human serum. DRV showed synergistic antiviral activity when studied in combination with the HIV PIs amprenavir, nelfinavir, or ritonavir, and additive antiviral activity when studied in combination with the PIs atazanavir, indinavir, lopinavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine, the NNRTIs delavirdine, efavirenz, etravirine, rilpivirine, or nevirapine, and the fusion inhibitor enfuvirtide. No antagonism was observed between DRV and any of those antiretrovirals.

Cobicistat: Cobicistat has no detectable antiviral activity in cell culture against HIV-1 and does not antagonize the antiviral activity of DRV, FTC, or TAF.

Emtricitabine: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and PBMCs. The EC_{50} values for FTC were in the range of 0.0013 to 0.64 µM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 µM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 µM). In two-drug combination studies of FTC with NRTIs (abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine), NNRTIs (delavirdine, efavirenz, nevirapine, and rilpivirine), PIs (amprenavir, nelfinavir, ritonavir, and saquinavir), and the integrase strand transfer inhibitor elvitegravir additive to synergistic effects were observed. No antagonism was observed for these combinations.

Tenofovir alafenamide: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/ macrophage cells, and CD4+ T lymphocytes. The EC_{50} values for TAF were in the range of 2.0 to 14.7 nM. TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM). In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic effects were observed. No antagonism was observed for these combinations.

Resistance *in vitro*

Darunavir: In vitro selection of DRV-resistant virus from wild-type HIV-1 was lengthy (>3 years). The selected viruses were unable to grow in the presence of DRV concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to DRV (range: 23- to 50-fold) harboured 2 to 4 amino acid mutations in the protease gene. The decreased susceptibility to DRV of the emerging viruses in the selection experiment could not be explained by the emergence of these protease mutations. *In vitro* selection of DRV-resistant HIV-1 (range: 53- to 641-fold change [FC] in EC_{50} values) from 9 HIV-1 strains harboring multiple PI RAMs resulted in the overall emergence of 22 mutations in the protease, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were present in more than 50% of the 9 darunavir-resistant isolates. A minimum of 8 of these DRV *in vitro* selected mutations, from which at least 2 were already present in the protease prior to selection, were required in the HIV-1 protease to render a virus resistant (FC >10) to DRV. In 1113 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir and in 886 baseline isolates from treatment-experienced patients, only the subgroups with >10 PI RAMs showed a median FC for darunavir >10.

In vivo, DRV RAMs (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V and L89V) in HIV-1 protease were derived from clinical trial data of antiretroviral therapy experienced patients, which were all protease inhibitor experienced patients.

Cobicistat: No in vitro resistance can be demonstrated due to its lack of antiviral activity.

Emtricitabine: HIV-1 isolates with reduced susceptibility to FTC have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 reverse transcriptase (RT).

Tenofovir alafenamide: HIV-1 isolates with reduced susceptibility to TAF have been selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R mutation in HIV-1 RT; in addition, a K70E mutation in HIV-1 RT has been transiently observed. HIV-1 isolates with the K65R mutation have low-level reduced susceptibility to abacavir, FTC, tenofovir, and lamivudine. *In vitro* drug resistance selection studies with TAF have shown no development of high-level resistance after extended culture.

Cross-resistance *in vitro*

Darunavir: Cross-resistance has been observed among HIV PIs. DRV has a <10-fold decreased susceptibility against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and/or tipranavir showing that viruses resistant to most PIs remain susceptible to DRV. Cross-resistance between DRV and the N(t)RTIs, the NNRTIs, the fusion inhibitors, CCR5 co-receptors agonists, or the integrase inhibitors is unlikely because the viral targets for those inhibitors are different.

Emtricitabine: FTC-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir, and zidovudine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine - thymidine analogue-associated mutations - (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E), or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N mutation or other mutations associated with resistance to NNRTIs was susceptible to FTC.

Tenofovir alafenamide: The K65R and K70E mutations result in reduced susceptibility to abacavir, didanosine, lamivudine, FTC, and tenofovir, but retain sensitivity to zidovudine. Multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M mutation complex including K65R showed reduced susceptibility to TAF. HIV-1 containing the K103N or Y181C mutations associated with resistance to NNRTIs were susceptible to TAF. HIV-1 containing mutations associated with resistance to PIs were susceptible to TAF.

Effects on electrocardiogram

Darunavir: In a four-way crossover trial, 40 healthy subjects were administered supratherapeutic doses of darunavir 1600 mg and ritonavir 100 mg once daily and darunavir 800 mg and ritonavir 100 mg twice daily (approximately 2 times the recommended darunavir dose) for seven days. When evaluating the 2-sided 90% CI on the time-matched mean changes in QTcF versus placebo, the upper bounds of both darunavir co-administered with ritonavir groups never exceeded the 10 ms boundary.

Cobicistat: The electrocardiographic effects of cobicistat were determined in a study of 48 healthy adult subjects. Cobicistat did not prolong the QTcF interval at doses of 250 mg and 400 mg, providing exposures 2- and 4-fold above the recommended therapeutic dose, respectively. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, 3 to 5 hours after dosing of cobicistat 250 mg. This finding was not considered to be clinically significant.

Emtricitabine: The effect of FTC on the QT interval is not known.

Tenofovir alafenamide: In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

Effects on serum creatinine

The effect of cobicistat on serum creatinine was investigated in a Phase 1 study in subjects with normal renal function ($eGFR_{CG}$ ≥80 mL/min, N=12) and mild to moderate renal impairment ($eGFR_{CG}$ 50-79 mL/min, N=18). A statistically significant change from baseline in $eGFR_{CG}$ was observed after 7 days of treatment with cobicistat 150 mg among subjects with normal renal function (9.9 ± 13.1 mL/min) and mild to moderate renal impairment (11.9 ± 7.0 mL/min). These decreases in $eGFR_{CG}$ were reversible after cobicistat was discontinued. The actual glomerular filtration rate, as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of cobicistat among subjects with normal renal function and mild to moderate renal impairment, indicating cobicistat inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual glomerular filtration rate.

An increase in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 0.4 mg per dL from baseline.

Clinical trials

The antiretroviral effect of SYMTUZA is due to the combined activity of darunavir, emtricitabine, and tenofovir alafenamide. The efficacy of SYMTUZA in HIV-1 treatment-naïve subjects and treatment-experienced subjects was evaluated in Phase 3 trials.

Efficacy in adult patients

HIV-1 treatment naïve patients

The efficacy of SYMTUZA in HIV-1 treatment-naïve subjects was evaluated in the Phase 3 trial TMC114FD2HTX3001 (AMBER) in which subjects were randomized in a 1:1 ratio to receive either SYMTUZA (N=362) or a combination fixed-dose combination of darunavir and cobicistat and fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate (F/TDF) (N=363) once daily until the last subject had reached Week 48. After Week 48 the trial was unblinded, with all subjects entering the open-label, single-group treatment phase with continued D/C/F/TAF use in the D/C/F/TAF group and switch to D/C/F/TAF in the control group. The median age was 34.0 years (range 18-71), 88.3% were male, 83.2% White, 11.1% Black, and 1.5% Asian. The mean baseline plasma HIV-1 RNA and the median baseline CD4+ cell count were 4.48 log_{10} copies/mL (range 1.3-6.7, 17.9% had a baseline viral load ≥100000 copies/mL) and 453.0 cells/mm^3 (range 38 to 1456 cells/mm^3), respectively. Virologic outcomes (ITT) reported in AMBER are shown in Table 7.

Table 7: Virologic Outcomes in AMBER at Week 48 and 96 (FDA Snapshot)

	Week 48		Week 96[e]
	SYMTUZA N=362	**D/C+F/TDF N=363**	**SYMTUZA N=362**
Virologic Response			
HIV-1 RNA <50 copies/mL	91.4%	88.4%	85.1%
Treatment difference[a]	2.7 (95% CI: -1.6; 7.1)		-
Virologic Failure[b]	4.4%	3.3%	5.5%
HIV-1 RNA ≥50 copies/mL	2.5%	2.5%	1.7%
Virologic Failure Leading to Discontinuation	0.3%	0	1.4%[d]

	Week 48		Week 96[e]
	SYMTUZA N=362	**D/C+F/TDF N=363**	**SYMTUZA N=362**
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL[e]	1.7%	0.8%	2.5%
No virologic data [c]	4.1%	8.3%	9.4%
Reasons			
Discontinued trial due to adverse event or death	2.2%	4.4%	2.2%
Discontinued trial for other reasons and last available HIV-1 RNA <50 copies/mL	1.1%	2.5%	5.8%
Missing data during window but on trial	0.8%	1.4%	1.4%
CD4+ cell count mean change from baseline	188.7	173.8	228.9

[a] Based on stratum adjusted MH test where stratification factors are HIV-1 RNA level (≤100,000 or > 100,000 copies/mL) and CD4+ cell count (< 200 or ≥200 cells/μL).

[b] Included subjects who had HIV-1 RNA ≥50 copies/mL in the Week 48/96 window; subjects who discontinued early due to lack or loss of efficacy per investigator's assessment; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a HIV-1 RNA ≥ 50 copies/mL.

[c] Week 48 window: Day 295 – Day 378; Week 96 window Day 631- Day 714

[d] Five subjects were discontinued from the study due to efficacy related reasons per investigator's assessment (physician decision), of which 3 had last on treatment HIV-1 RNA <50 copies/mL.

[e] No comparator data available beyond Week 48 because after Week 48 the trial was unblinded, with all the subjects entering the open-label, single-group treatment phase.

Changes in measures of bone mineral density

In the phase 3 study TMC114FD2HTTX3001 in treatment-naïve patients, SYMTUZA was associated with no relevant changes in bone mineral density (BMD) compared to decreases in the control group (DRV/COBI+F/TDF) as measured by DXA analysis of hip (LS means percent change: 0.17% vs -2.69%, p < 0.001) and lumbar spine (LS means percent change: -0.68%vs -2.38%, p=0.004) after 48 weeks of treatment.After 96 weeks of treatment with SYMTUZA, the LS means percent changes (95% CI) from baseline in BMD at the hip and spine region were respectively: -0.26 (-0.96; 0.45) % and -0.93 (-1.82; -0.05) %.

In the phase 3 study TMC114IFD3013 in treatment experienced patients, improvements in BMD were noted at 48 weeks after switching to SYMTUZA from a TDF-containing regimen compared to maintaining the TDF-containing regimen. After 96 weeks of treatment with SYMTUZA, further improvements in BMD were noted when compared to baseline.

Changes in measures of renal function

In studies in treatment-naïve patients, SYMTUZA was associated with a lower impact on renal safety parameters (as measured after 48 weeks treatment by estimated glomerular filtration rate by Cockcroft-Gault method) compared to control group (DRV/COBI+F/TDF) (see **section 4.4** Special warnings and precautions for use). In the SYMTUZA group, there was an improvement of proteinuria (as measured by urine protein to creatinine ratio and urine albumin to creatinine ratio) at Week 48 vs. baseline as compared to the control group that used a tenofovir disoproxil fumarate (TDF) based regimen. Through 48 weeks of treatment, no subject discontinued SYMTUZA due to a treatment-emergent renal adverse event.

An improved renal safety profile was maintained through Week 48 in subjects who switched to SYMTUZA compared with those who stayed on a TDF-containing regimen. In the Phase 3 clinical trials of SYMTUZA including treatment-naïve and treatment-experienced subjects, there were no cases of proximal renal tubulopathy, including Fanconi syndrome, reported in the SYMTUZA group through Week 96.

Clinical Trial Results in HIV-1 Virologically-Suppressed Subjects Who Switched to SYMTUZA

Phase 3 trial TMC114IFD3013 (EMERALD) evaluated the efficacy of SYMTUZA in virologically-suppressed (HIV-1 RNA less than 50 copies/mL) HIV-1 infected subjects. Subjects were virologically suppressed for at least 2 months and no more than once had a viral load elevation above 50 HIV-1 RNA copies/mL during the year prior to enrollment. Patients were allowed in the study if they had previous failure on any non-darunavir ARV regimen. Patients had no history of virologic failure on darunavir-based regimens, and if historical genotypes were available, absence of darunavir RAMs. Subjects were on a stable antiretroviral regimen (for at least 6 months), consisting of a boosted protease inhibitor [either darunavir once daily or atazanavir (both boosted with ritonavir or cobicistat), or lopinavir with ritonavir] combined with emtricitabine and TDF. They either switched to SYMTUZA (N=763) or continued their treatment regimen (N=378) (randomized 2:1). Subjects had a median age of 46 years (range 19-78), 82% were male, 75.5% White, 20.9% Black, and 2.3% Asian. The median baseline CD4+ cell count was 628 × 10^6 cells/mm^3 (range 111-1921 × 10^6 cells/mm^3). Virologic outcomes (ITT) reported in EMERALD are shown in Table 8.

Table 8: Week 48 and 96 Virologic Outcomes in EMERALD Trial

	Week 48		Week 96[g]
	SYMTUZA N=763	**bPI+F/TDF N=378**	**SYMTUZA N=763**
Cumulative Protocol-Defined Virologic Rebound[a]			
Protocol Defined Rebound Rate	2.5%	2.1%	3.1%
(95% CI)[b]	(1.5; 3.9)	(0.9; 4.1)	(2.0 ; 4.6)
Difference in Proportions	0.4 (95% CI: -1.5; 2.2)		-
FDA Snapshot Outcome			
HIV-1 RNA <50 copies/mL	94.9%	93.7%	90.7%
Virologic Failure[c]	0.8%	0.5%	1.2%
Treatment difference[d]	0.3 (95% CI: -0.7; 1.2)		-
HIV-1 RNA ≥50 copies/mL	0.5%	0.5%	0.7%[f]
Virologic failure - leading to discontinuation	0	0	0
Virologic failure - discontinued due to other reason and last available HIV-1 RNA ≥50 copies/mL	0.3%	0	0.5%
No virologic data [e]	4.3%	5.8%	8.1%
Reasons			
Discontinued trial due to adverse event or death	1.4%	1.1%	2.4%
Discontinued trial for other reasons and last available HIV-1 RNA <50 copies/mL	2.5%	4.2%	5.0%
Missing data during window but on trial	0.4%	0.5%	0.8%

[a] 2 consecutive HIV-1 RNA ≥ 50 copies/mL, or in case of discontinuation or at Week 48/96 for any reason, (single) HIV-1 RNA ≥ 50 copies/mL as of baseline (included)

[b] Two-sided Exact Clopper-Pearson 95% CI

[c] Included subjects who had ≥50 copies/mL in the Week 48/96 window; subjects who discontinued early due to lack or loss of efficacy per investigator's assessment; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value ≥ 50 copies/mL.

[d] Based on MH test adjusting for bPI at screening (ATV with rtv or COBI, DRV with rtv or COBI, LPV with rtv).

[e] Week 48 window: Day 295 – Day 378; Week 96 window: Day 631 – Day 714

[f] The following viral load values were observed for these subjects at Week 96: 54 copies/mL, 78 copies/mL, 111 copies/mL, 152 copies/mL, and 210 copies/mL.

[g] No comparator data available beyond Week 48.

Efficacy in paediatric patients

The efficacy of SYMTUZA in paediatric patients has not been investigated. However, the use of SYMTUZA in adolescent patients from the age of 12 years to <18 years, and weighing at least 40 kg is supported by two clinical studies in HIV-1 infected paediatric patients: TMC114-C230 and GS-US-292-0106. (For more details, refer to the Product Information of darunavir and the fixed-dose combinations of emtricitabine/tenofovir alafenamide and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.)

The open-label, Phase 2 trial TMC114-C230 was conducted for evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir with low dose ritonavir in 12 treatment-naïve HIV-1 infected paediatric patients aged 12 to less than 18 years and weighing at least 40 kg. These patients received darunavir/ritonavir 800/100 mg once daily in combination with other antiretroviral agents. Virologic response was defined as HIV-1 RNA < 50 copies/mL at Week 48. Patients had a median age of 14.4 years (range: 12.6-17.3), and 66.7% were female, 58.3% were White, and 41.7% were Black. At baseline, median plasma HIV-1 RNA was 4.92 $\log_{10}$ copies/mL (range: 3.56-5.52), median CD4+ cell count was 282 × 10^6 cells/L (range: 204-515 × 10^6 cells/L), and median CD4+ % was 18.3% (range: 12.1-40.8%). Overall, 41.7% had baseline plasma HIV-1 RNA ≥100000 copies/mL. Table 9 shows the virologic outcomes of study TMC114-C230 at Week 48. No emergent resistance to darunavir was detected through Week 48.

Table 9: Virologic Outcomes of Trial TMC114-C230 at Week 48

	Darunavir/ritonavir (N=12)
HIV-1 RNA < 50 copies/mL (FDA Snapshot)	91.7% (11)
HIV-1 RNA < 50 copies/mL (TLOVR)	83.3% (10)
≥1.0 $\log_{10}$ decrease from baseline in HIV-1 RNA[a]	100%
CD4+ cell count mean change from baseline[a]	221

[a] Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0.

In the open-label study GS-US-292-0106, the efficacy, safety, and pharmacokinetics of emtricitabine and tenofovir alafenamide were evaluated in 50 HIV-1 infected, treatment-naïve adolescents receiving emtricitabine and tenofovir alafenamide (10 mg) together with elvitegravir and cobicistat as a fixed-dose combination tablet. Patients had a median age of 15 years (range: 12-17), and 56% were female, 12% were Asian, and 88% were Black. At baseline, median plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL (range: 3.25-6.50), median CD4+ cell count was 456 cells/mm^3 (range: 95-1110), and median CD4+ % was 23% (range: 7-45%). Overall, 22% had baseline plasma HIV-1 RNA >100000 copies/mL. At 48 weeks, 92% (46/50) achieved HIV-1 RNA <50 copies/mL (FDA Snapshot), similar to response rates in studies of treatment-naïve HIV-1 infected adults. The mean increase from baseline in CD4+ cell count at Week 48 was 224 cells/mm^3. No emergent resistance to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide was detected through Week 48.

In vivo selection of viral resistance during SYMTUZA therapy, treatment naïve or virologically suppressed patients

Over 96 weeks of treatment in the Phase 3 studies TMC114FD2HTX3001 (AMBER) in treatment-naïve patients and TMC114IFD3013 (EMERALD) in virologically suppressed treatment-experienced patients, resistance testing was performed on samples from patients experiencing protocol-defined virologic failure (PDVF) and who had HIV-1 RNA ≥400 copies/mL at failure or at later time points. Emerging resistance in the SYMTUZA groups is shown in Table 10. No DRV, primary PI, or TDF/TAF resistance-associated mutations were observed.

Table 10: Emerging Resistance in AMBER and EMERALD Trials (Week 96)

Study	Treatment group	Subjects, n	Subjects with PDVF, n (%)	Subjects with PDVF evaluated for resistance, n (%)	Subjects with ≥1 emergent RAM, n (%)		
					Protease	Reverse transcriptase	
					Primary PI/DRV	TDF/TAF	FTC
TMC114FD2HTX3001	SYMTUZA	362	15 (4.1)	9 (2.5)	0	0	1 M184I/V[a]
TMC114IFD3013	SYMTUZA	763	24 (3.1)	4 (0.5)	0	0	0
Total Phase 3	SYMTUZA	1,125	39 (3.5)	13 (1.2)	0	0	1 (0.1)

[a] At Week 36 M184M/I/V observed, conferring resistance to FTC. This subject harbored a K103N mutation at screening, indicating transmitted NNRTI resistance.
DRV = darunavir; FTC = emtricitabine; PDVF = protocol-defined virologic failure; PI = protease inhibitor; RAM = resistance-associated mutation; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide

In vivo cross-resistance in HIV-1 infected, treatment naïve or virologically suppressed patients

The emtricitabine-resistant virus with the M184M/IV substitution was cross-resistant to lamivudine, but retained sensitivity to abacavir, stavudine, tenofovir, and zidovudine.

For more details on the clinical resistance profile of darunavir, boosted with ritonavir or cobicistat, and emtricitabine/tenofovir alafenamide please refer to the respective Product Information.

5.2 PHARMACOKINETIC PROPERTIES

The bioavailability of all components of SYMTUZA was comparable to that when DRV 800 mg, COBI 150 mg, and FTC/TAF 200/10 mg were co-administered as separate formulations; bioequivalence was established following single-dose administration under fed conditions in healthy subjects (N=96). The bioavailability of the components of SYMTUZA was not affected when administered orally as a split tablet compared to administration as a tablet swallowed whole.

Absorption

The absolute bioavailability of a single 600 mg dose of DRV alone was approximately 37% and increased to approximately 82% in the presence of ritonavir. The absolute bioavailability of the FTC 200 mg capsule was 93%.

All components were rapidly absorbed following oral administration of SYMTUZA in healthy subjects. Maximum plasma concentrations of DRV, COBI, FTC, and TAF were achieved at 4.00, 4.00, 2.00, and 1.50 hours after dosing, respectively.

The exposure (AUC) of DRV and COBI administered as SYMTUZA was 34% and 29% lower, respectively, in fasted condition compared to fed condition. For FTC and TAF, exposure was comparable in fed and fasted conditions. Therefore, SYMTUZA should be taken with food. The type of food does not affect exposure to SYMTUZA.

Distribution

Darunavir: DRV is approximately 95% bound to plasma proteins and binds primarily to plasma alpha-1-acid glycoprotein.

Cobicistat: Cobicistat is 97% to 98% bound to human plasma proteins and the mean plasma to blood-drug concentration ratio was approximately 2.

Emtricitabine: In vitro binding of FTC to human plasma proteins was <4% and independent of concentration over the range of 0.02 to 200 mcg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

Tenofovir alafenamide: In vitro binding of tenofovir to human plasma proteins is less than 0.7% and is independent of concentration over the range of 0.01 to 25 mcg/mL. *Ex-vivo* binding of TAF to human plasma proteins in samples collected during clinical studies was approximately 80%. Distribution studies in dogs showed 5.7- to 15-fold higher ^{14}C-radioactivity in lymphoid tissues (iliac, axillary, inguinal and mesenteric lymph nodes, and spleen) 24 hours following administration of an equivalent dose of ^{14}C-TAF relative to ^{14}C-TDF.

Metabolism

Darunavir: In vitro experiments with human liver microsomes indicate that DRV primarily undergoes oxidative metabolism. DRV is extensively metabolized by the hepatic CYP system and almost exclusively by isozyme CYP3A. A ^{14}C-darunavir trial in healthy volunteers showed that a majority of the radioactivity in plasma after a single 400/100 mg DRV/rtv dose was due to the parent drug. At least 3 oxidative metabolites of DRV have been identified in humans; all showed activity that was at least 10-fold less than the activity of DRV against wild-type HIV.

Cobicistat: Cobicistat is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation.

Emtricitabine: Following administration of ^{14}C-FTC, complete recovery of the FTC dose was achieved in urine (~86%) and faeces (~14%). Thirteen percent of the dose was recovered in the urine as three putative metabolites. The biotransformation of FTC includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Tenofovir alafenamide: Metabolism is a major elimination pathway for TAF in humans, accounting for >80% of an oral dose. *In vitro* studies have shown that TAF is metabolized to tenofovir (major metabolite) by cathepsin A in PBMCs (including lymphocytes and other HIV target cells) and macrophages; and by carboxylesterase-1 in hepatocytes. *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. In human clinical studies, a 10 mg oral dose of TAF resulted in tenofovir diphosphate concentrations >4-fold higher in PBMCs and >90% lower concentrations of tenofovir in plasma as compared to a 300 mg oral dose of TDF. *In vitro*, TAF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is minimally metabolized by CYP3A4. Upon co-administration with the moderate CYP3A inducer probe efavirenz, TAF exposure was not significantly affected.

Excretion

Darunavir: After a 400/100 mg ^{14}C-DRV/rtv dose, approximately 79.5% and 13.9% of the administered dose could be retrieved in faeces and urine, respectively. Unchanged DRV accounted for approximately 41.2% and 7.7% of the administered dose in faeces and urine, respectively. The intravenous clearance of DRV alone (150 mg) and in the presence of low dose ritonavir was 32.8 L/h and 5.9 L/h, respectively. The terminal elimination half-life of DRV is approximately 6 hours following administration of SYMTUZA.

Cobicistat: Following oral administration of ^{14}C-cobicistat, 86% and 8.2% of the dose were recovered in faeces and urine, respectively. The terminal elimination half-life of cobicistat is approximately 3 to 4 hours following administration of SYMTUZA.

Emtricitabine: FTC is primarily excreted by the kidney, by both glomerular filtration and active tubular secretion. Following administration of SYMTUZA, the elimination half-life of FTC is approximately 17 hours.

Tenofovir alafenamide: TAF is mainly eliminated following metabolism to tenofovir. The terminal elimination half-life of TAF is approximately 0.3 hours following administration of SYMTUZA. Tenofovir is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Tenofovir has a median plasma elimination half-life of approximately 32 hours. Renal excretion of intact TAF is a minor pathway with less than 1% of the dose eliminated in urine. The pharmacologically active metabolite, tenofovir diphosphate, has an elimination half-life of approximately 150-180 hours within PBMCs.

Special populations

Paediatrics (17 years of age and younger)

SYMTUZA has not been investigated in paediatric patients. However, available pharmacokinetic data for the different components of SYMTUZA indicate that doses of 800 mg darunavir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide result in similar exposures in adolescents aged 12 years and older, weighing at least 40 kg, and adults.

Darunavir: A dosage of 800 mg once daily in paediatric patients weighing ≥40 kg resulted in darunavir exposure that was comparable to that achieved in adults receiving the same dose.

Cobicistat: Exposures of cobicistat 150 mg achieved in paediatric patients aged 12 to <18 years were similar to exposures achieved in treatment-naïve adults.

Emtricitabine and *tenofovir alafenamide:* Exposures of FTC 200 mg and TAF 10 mg achieved in paediatric patients aged 12 to <18 years were similar to exposures achieved in treatment-naïve adults.

Elderly (65 years of age and older)

Population pharmacokinetic analysis in HIV infected patients showed that DRV pharmacokinetics are not different in the age range evaluated (18 to 75 years).

No clinically relevant pharmacokinetic differences due to age have been identified for cobicistat, emtricitabine, or tenofovir alafenamide.

Renal impairment

The pharmacokinetics of SYMTUZA have not been investigated in patients with renal impairment. However, there are data for the components of SYMTUZA.

Darunavir: Results from a mass balance study with ^{14}C-DRV/rtv showed that approximately 7.7% of the administered dose of DRV is excreted in the urine as unchanged drug. Although DRV has not been studied in patients with renal impairment, population pharmacokinetic analysis showed that the pharmacokinetics of DRV were not significantly affected in HIV infected patients with moderate renal impairment ($eGFR_{CG}$ between 30-60 mL/min, N=20).

Cobicistat: A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with severe renal impairment ($eGFR_{CG}$ <30 mL/min). No meaningful differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat.

Emtricitabine: Mean systemic FTC exposure was higher in patients with severe renal impairment ($eGFR_{CG}$ <30 mL/min) than in subjects with normal renal function.

Tenofovir alafenamide: No clinically relevant differences in TAF or tenofovir pharmacokinetics were observed between healthy subjects and subjects with severe renal impairment ($eGFR_{CG}$ <30 mL/min) in studies of TAF. There are no pharmacokinetic data on TAF in patients with $eGFR_{CG}$ <15 mL/min.

Hepatic impairment

The pharmacokinetics of SYMTUZA have not been investigated in patients with hepatic impairment. However, there are data for the components of SYMTUZA.

Darunavir: DRV is primarily metabolized and eliminated by the liver. In a multiple-dose study with DRV/rtv (600/100 mg) twice daily, it was demonstrated that the steady-state pharmacokinetic parameters of DRV in subjects with mild (Child-Pugh Class A, N=8) and moderate (Child-Pugh Class B, N=8) hepatic impairment were comparable with those in healthy subjects. The effect of severe hepatic impairment on the pharmacokinetics of DRV has not been studied.

Cobicistat: Cobicistat is primarily metabolized and eliminated by the liver. A study of the pharmacokinetics of cobicistat was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. No dosage adjustment of cobicistat is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of cobicistat has not been studied.

Emtricitabine: The pharmacokinetics of FTC have not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

Tenofovir alafenamide: Clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were not observed in patients with mild, moderate, or severe hepatic impairment; no TAF dose adjustment is required in patients with hepatic impairment.

Hepatitis B and/or hepatitis C virus co-infection

There were insufficient data in clinical trials on the pharmacokinetics of its components to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of SYMTUZA.

Darunavir: In HIV infected subjects taking DRV/rtv, the 48 week analysis of the data from Phase 3 clinical studies indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of DRV.

Cobicistat: There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of cobicistat.

Emtricitabine and tenofovir alafenamide: Pharmacokinetics of FTC and TAF have not been fully evaluated in patients co-infected with hepatitis B and/or C virus.

Pregnancy and postpartum

The exposure to total darunavir boosted with cobicistat after intake of darunavir/cobicistat 800/150 mg q.d. as a fixed-dose combination tablet was substantially lower during the second and third trimesters of pregnancy compared with 6-12 weeks postpartum (see **Table 11**). The decrease in unbound (i.e., active) darunavir pharmacokinetic parameters (C_{max} and AUC_{24h}) during pregnancy compared to postpartum was less pronounced than for total darunavir.

Table 11: Pharmacokinetic Results of Total Darunavir after Administration of Darunavir/Cobicistat 800/150 mg q.d. as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy, and Postpartum

Pharmacokinetics of total darunavir (mean ± SD)	2nd Trimester of pregnancy N=7	3rd Trimester of pregnancy N=6	Postpartum N=6
C_{max}, ng/mL	4340 ± 1616	4910 ± 970	7918 ± 2199
AUC_{24h}, ng.h/mL	47293 ± 19058	47991 ± 9879	99613 ± 34862
C_{min}, ng/mL	168 ± 149	184 ± 99	1538 ± 1344

In women receiving darunavir/cobicistat 800/150 mg q.d. during the 2nd trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the 3rd trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum.

No pharmacokinetic data are available for emtricitabine and tenofovir alafenamide during pregnancy.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Darunavir: DRV was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reverse mutation (Ames), chromosomal aberration in human lymphocytes, and *in vivo* micronucleus test in mice.

Cobicistat: Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma, or rat micronucleus assays.

Emtricitabine: Emtricitabine was not mutagenic in bacteria or mouse lymphoma cell assays *in vitro* nor clastogenic in the mouse micronucleus test *in vivo*.

Tenofovir alafenamide: TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma, or rat micronucleus assays.

Carcinogenicity

Darunavir: DRV was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450, and 1000 mg/kg were administered to mice and doses of 50, 150, and 500 mg/kg were administered to rats. Dose-related increases in the incidences of hepatocellular adenomas and carcinomas were observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of DRV did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of DRV to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures (based on AUC) to DRV were between 0.5- and 0.6-fold (mice) and was 0.9-fold (rats), relative to those observed in humans at the recommended therapeutic dose.

Cobicistat: In a long-term study in mice with doses of up to 50 mg/kg/day in males and 100 mg/kg/day in females (9-21 times the human exposure (AUC) at 150 mg daily), cobicistat treatment did not result in any increased tumour incidences. In a corresponding study in rats, with doses of up to 50 mg/kg/day in males and 30 mg/kg/day in females (2.6 and 2.3 times the human exposure

with 150 mg daily), treatment resulted in increased incidence of thyroid follicular cell tumours. Hepatocyte hypertrophy was also observed, and this oncogenic response is most likely related to alterations in thyroid hormones and to be specific to species.

Emtricitabine: In long-term carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (26 times the human systemic exposure at the recommended dose of emtricitabine in SYMTUZA®) or in rats at doses up to 600 mg per kg per day (31 times the human systemic exposure at the recommended dose). Therefore, emtricitabine had demonstrated low carcinogenic potential in mice and rats.

Tenofovir alafenamide: Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of tenofovir disoproxil fumarate for HIV-1 infection. At the high dose in female mice, liver adenomas were increased at exposures ~ 10 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 4 times that observed in humans at the therapeutic dose.

Toxicology

Darunavir: Animal toxicology studies have been conducted with DRV alone in mice, rats, and dogs, and in combination with ritonavir in rats and dogs. In chronic toxicology studies in rats and dogs, there were only limited effects of treatment with DRV. In the rat, the key target organs identified were the hematopoietic system, the blood coagulation system, liver, and thyroid, observed at 100 mg/kg/day and above and at exposures below clinical levels. A variable but limited decrease in red blood cell-related parameters was observed, together with increases in activated PTT. The observed liver and thyroid changes were considered to reflect an adaptive response to enzyme induction in the rat rather than an adverse effect. In combination toxicity studies with ritonavir, no additional target organs of toxicity were reported in rats. In the dog, no major toxicity findings or key target organs were identified at doses up to 120 mg/kg/day and exposures equivalent to clinical exposure at the recommended dose.

Cobicistat: Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity. *Ex vivo* rabbit studies and *in vivo* dog studies suggest that cobicistat has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than the human exposure at the recommended 150 mg daily dose.

Emtricitabine: Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Tenofovir alafenamide: Non-clinical studies in rats and dogs revealed bone and kidney as the primary target organs of toxicity. Bone toxicity was observed as reduced bone mineral density.

Juvenile toxicity

In a pre- and postnatal development assessment in rats, DRV with and without ritonavir caused a transient reduction in body weight gain of the offspring during lactation. This was attributed to drug exposure via the milk. No post weaning functions were affected with DRV alone or in combination with ritonavir. In juvenile rats directly dosed with DRV (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age, mortality was observed and, in some of the animals, convulsions. Within this age range, exposures in plasma, liver, and brain were dose and age dependent and were considerably higher than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of DRV and the immaturity of the blood brain

barrier. No treatment related mortalities were noted in juvenile rats dosed at 1000 mg/kg DRV (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats. Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, DRV should not be used in paediatric patients below 3 years of age.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core

Croscarmellose sodium
Magnesium stearate
Microcrystalline cellulose
Silicon dioxide*

*cobicistat is absorbed on a silicon dioxide carrier

Film-coat

OPADRY® II complete film coating system 85F120020 YELLOW (ARTG PI No. 114529)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep out of the sight and reach of children. Store in the original packaging to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

SYMTUZA tablets are supplied in a white, high density polyethylene (HDPE) bottle and a polypropylene child-resistant closure. Each bottle contains 30 tablets and a desiccant.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

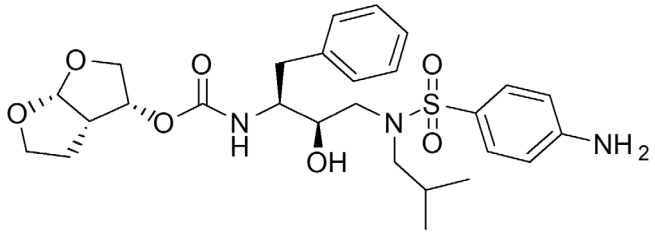
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Darunavir

The chemical name for darunavir is [(1S,2R)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester.

Darunavir has the following structural formula:



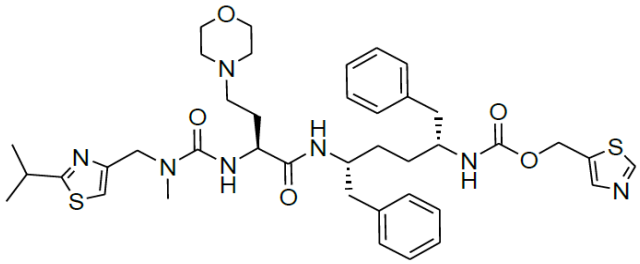
It has an empirical formula of $C_{27}H_{37}N_3O_7S$ and a molecular weight of 547.66.

Darunavir is isolated as darunavir ethanolate, a pseudo-polymorphic form of darunavir. Darunavir ethanolate is a white to off-white powder that is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol, and freely soluble in acetone and dichloromethane. The partition coefficient (*log p*) for darunavir is 2.47 and the dissociation constant, pKa, is 2.02.

Cobicistat

The chemical name for cobicistat is 1,3-Thiazol-5-ylmethyl [(2*R*,5*R*)-5-{[(2*S*)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate.

Cobicistat has the following structural formula:



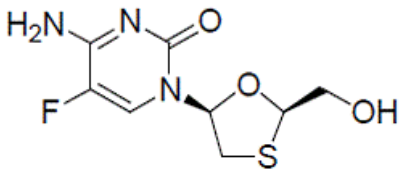
It has an empirical formula of $C_{40}H_{53}N_7O_5S_2$ and a molecular weight of 776.0.

Cobicistat is a white to pale yellow solid with a solubility of 0.1 mg/mL in water at 20 °C. The partition coefficient (*log p*) for cobicistat is 4.3 and the pKa is 6.4.

Emtricitabine

The chemical name of FTC is 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine. FTC is the (-) enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5-position.

Emtricitabine has the following structural formula:



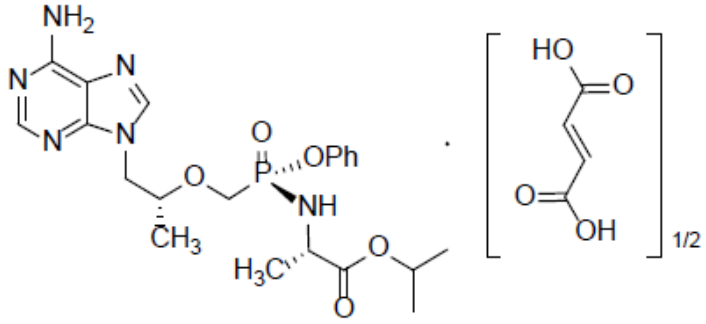
It has an empirical formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.2.

FTC is a white to off-white crystalline powder with a solubility of approximately 112 mg per mL in water at 25°C. The partition coefficient (log p) for emtricitabine is -0.43 and the pKa is 2.65.

Tenofovir alafenamide fumarate

The chemical name of TAF is L-Alanine, *N*-[(*S*)-[[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2*E*)-2-butenedioate (2:1).

TAF has the following structural formula:



It has an empirical formula of $C_{21}H_{29}O_5N_6P \cdot ½(C_4H_4O_4)$ and a molecular weight of 534.50.

TAF is a white to off-white or tan powder with a solubility of 4.7 mg per mL in water at 20 °C.

CAS NUMBERS

Darunavir: 206361-99-1
Cobicistat: 1004316-88-4
Emtricitabine: 143491-57-0
Tenofovir alafenamide: 379270-37-8 and tenofovir alafenamide fumarate: 1392275-56-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

NZ Office: Auckland New Zealand

9. DATE OF FIRST APPROVAL

22 November 2019

10. DATE OF REVISION

27 March 2023

Summary table of changes

Section changed	Summary of new information
4.4 and 4.8	Removal of text regarding fat redistribution and lipodystrophy
4.5	Revision to co-administration with dabigatran etexilate